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Modelling corticothalamic feedback and the gating of the thalamus by the cerebral cortex

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Abstract – Morphological studies have shown that excitatory synapses from the cortex constitute the major source of synapses in the thalamus. However, the effect of these corticothalamic synapses on the function of the thalamus is not well understood because thalamic neurones have complex intrinsic firing properties and interact through multiple types of synaptic receptors. Here we investigate these complex interactions using computational models. We show first, using models of reconstructed thalamic relay neurones, that the effect of corticothalamic synapses on relay cells can be similar to that of afferent synapses, in amplitude, kinetics and timing, although these synapses are located in different regions of the dendrites. This suggests that cortical EPSPs may complement (or predict) the afferent information. Second, using models of reconstructed thalamic reticular neurones, we show that high densities of the low-threshold Ca^{2+} current in dendrites can give these cells an exquisite sensitivity to cortical EPSPs, but only if their dendrites are hyperpolarized. This property has consequences at the level of thalamic circuits, where corticothalamic EPSPs evoke bursts in reticular neurones and recruit relay cells predominantly through feedforward inhibition. On the other hand, with depolarized dendrites, thalamic reticular neurones do not generate bursts and the cortical influence on relay cells is mostly excitatory. Models therefore suggest that the cortical influence can either promote or antagonize the relay of information, depending on the state of the dendrites of reticular neurones. The control of these dendrites may therefore be a determinant of attentional mechanisms. We also review the effect of corticothalamic feedback at the network level, and show how the cortical control over the thalamus is essential in co-ordinating widespread, coherent oscillations. We suggest mechanisms by which different modes of corticothalamic interaction would allow oscillations of very different spatiotemporal coherence to coexist in the thalamocortical system. © 2000 Elsevier Science Ltd. Published by Éditions scientifiques et médicales Elsevier SAS

corticofugal / feedback / computational model / attention / oscillations

1. Introduction

One of the most intriguing feature of thalamic circuits is that, in addition to providing a relay of afferent inputs to cerebral cortex, they are massively innervated by fibres arising from the cortex itself [32, 39]. This corticothalamic projection provides the major source of excitatory synapses on thalamic neurones and in particular, corticothalamic synapses largely outnumber afferent synapses [29, 30, 44, 45]. The notion of the thalamus as a relay station, linking the periphery to the cerebral cortex, should clearly be revised in the light of these morphological data. The cortex might be the region that is the most influential on the activity of the thalamus, but this influence is too often neglected.

The study of thalamo-cortical interactions began several decades ago with the recordings of oscillatory behaviour, for which the thalamus has been shown to play a key role [2, 6, 60]. Although an active role of the cortex was claimed more than 50 years ago [8, 50], early studies have most often considered the cortex as passively driven by a 'thalamic pacemaker'. The pacemaker properties of the thalamus have indeed been demonstrated, by isolating thalamic circuits in vivo [61] or in vitro [70]. However, in the intact brain, it was found that thalamic oscillations are triggered by the cortex [65] and that the corticothalamic feedback projection is essential in co-ordinating widespread, coherent, synchronized oscillations in different thalamic nuclei [14]. It thus appears that, rather than providing an autonomous, independent drive, the thalamic pacemakers are controlled and co-ordinated by the cortex.

This notion of cortical control of thalamic-generated oscillations has allowed computational models to account for a large spectrum of experimental data obtained in vivo and in vitro, ranging from ion channel, cellular and network aspects of the genesis of oscillations (reviewed in [21]). In

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addition, this notion also accounts for the genesis of pathological behaviour such as absence seizures [19], which cannot be understood without considering the influence of the cortex over the thalamus [31].

The role of the corticothalamic projection has also been extensively studied in sensory processing [56, 59]. The activation of corticothalamic synapses have clear facilitatory effects on the relay of information to the cerebral cortex [1, 42, 57, 59, 71, 73]. It also seems indispensable to control the time locking of thalamic neurones into fast oscillations in the gamma frequency range (20–60 Hz) during visual processing [54, 58]. However, besides this excitatory effect, there are also numerous evidences that the cortex evokes a dominant inhibition in thalamic relay cells [1, 10, 12, 18, 43, 55, 73].

To understand the exact effect of corticothalamic feedback on thalamic circuits, one must consider the different types of thalamic neurones and their synaptic interactions (schematized in *figure 1*). Thalamic neurones are characterized by complex intrinsic firing properties, which may range from the genesis of high-frequency bursts of action potential to tonic firing [64]. Their synaptic interactions also involve different types of receptors which mediate both fast and slow interactions. In addition, it has been shown that cortical and afferent synapses are segregated in different regions of the dendrites of thalamic relay neurones [44], which may strongly affect their impact on cellular responsiveness. Taken together, these data indicate that the effect of cortical synapses on thalamic circuits is complex and difficult to predict intuitively. Here we investigate these interactions using computational models.

2. Materials and methods

Computational models were based on several previously published papers in which all details have been described [23, 24, 27, 28]. All simulations were done using the NEURON simulation environment [35, 36].

2.1. Cellular models

Computational models of thalamic relay and reticular neurones were based on cellular morphologies obtained in two previous studies [23, 28]. These neurones (*figure 2*) were intracellularly recorded in slices from rat ventrobasal nucleus and stained with biocytin [38]. Their morphology was reconstructed in 3-D using a computerized camera-lucida system and then incorporated into NEURON to simulate the cable equations of these 3-D morphologies. The methods were detailed previously (see [23, 28]).

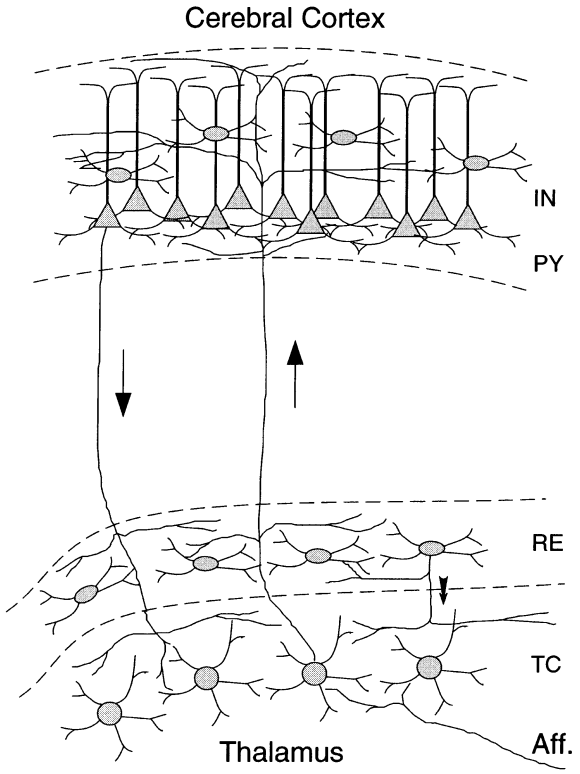

Figure 1. Cell types and connectivity in the thalamocortical network. Four cell types and their connectivity are indicated: thalamocortical (TC) relay cells, thalamic reticular (RE) neurones, cortical pyramidal cells (PY) and interneurones (IN). TC cells receive prethalamic afferent connections (Aff.), which may be sensory afferents in the case of specific thalamic nuclei involved in vision, audition and somatosensory modalities. This information is relayed to the corresponding area of cerebral cortex through ascending thalamocortical fibres (upward arrow). These fibres leave collaterals within the RE nucleus on the way to the cerebral cortex, where they arborize in superficial layers I and II, layer IV and layer VI. Corticothalamic feedback is mediated primarily by a population of layer VI PY neurones that project to the thalamus. The corticothalamic fibres (downward arrow) give collaterals within the RE nucleus and relay nuclei. RE cells form an inhibitory network that surrounds the thalamus, receive a copy of nearly all thalamocortical and corticothalamic activity, and project inhibitory connections solely to neurones in the thalamic relay nuclei. Projections between TC, RE and PY cells are usually organized topographically such that each cortical column is associated with a given sector of thalamic TC and RE cells. Modified from [24].

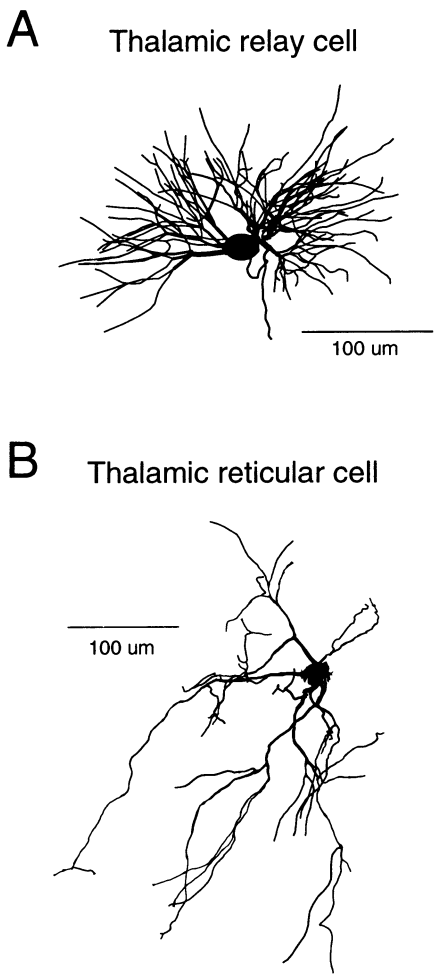

Figure 2. Dendritic morphology of two thalamic cell types used in computational models. Thalamic relay cell (**A**) and thalamic reticular neurone (**B**) from rat ventrobasal nucleus, which were intracellularly recorded in slices and stained with biocytin [38]. Their morphology was reconstructed in 3-D using a computerized camera-lucida system [23, 28]. This information was then used to build computational models incorporating the cable equations of these 3-D morphologies based on the experimental data. Because models and data correspond to the same morphology, this approach is particularly powerful to estimate the somato-dendritic distribution of conductances in the cell (see [23, 28]).

Passive properties were obtained by fitting the model to passive responses obtained in voltage-clamp. Because models and recordings correspond to the same cellular morphology, this method allows accurate estimation of the passive parameters. Active currents (I_{Na}, I_{Kd}, I_T) were modelled by Hodgkin-Huxley [37] type kinetic models (see details in [23, 28]).

Synaptic inputs were simulated by kinetic models of AMPA, NMDA, $GABA_A$ and $GABA_B$ receptors developed previously [27]. Synapses were located exclusively in the dendrites as described in the text. Synaptic inputs were either simulated in an isolated dendritic branch, or were distributed in an entire dendritic region according to the path distance from soma. For example, to localize cortical inputs in the distal third of thalamic relay cell dendrites, excitatory synapses were distributed in all dendritic segments with path distance >100 μm. The conductance of each synapse was scaled to the area of the dendritic segment, such that a constant density of conductance was simulated in the distal region (see text for conductance values). All excitatory conductance values are given for AMPA receptors; the NMDA conductance was set to 25% of the AMPA conductance.

2.2. Network models

A thalamocortical network consisting of four one-dimensional layers of cortical and thalamic cells was simulated (same cell types as in *figure 1*). The network included 100 thalamic relay cells (TC), 100 thalamic reticular (RE) neurones, 100 cortical pyramidal (PY) cells and 100 cortical interneurones (IN). The thalamus was represented by two homogeneous population of cells (TC and RE), with no interneurones[1]. These two cell types established topographic connections; each neurone densely projected to neurones of the other layer within a focal region of a radius of five cells (see details in [22]).

The cortex was represented by a simplified representation of layer VI, in which PY cells constitute the major source of corticothalamic fibres. As these corticothalamic cells receive a significant proportion of their excitatory synapses directly from ascending thalamic axons [34, 72], these cells mediate a monosynaptic excitatory feedback loop (thalamus-cortex-thalamus), which was modelled here. This representation of layer VI was organized in one dimension with mixed PY and IN cells, which connections were local and topographically orga-

[1] This configuration was inspired from recordings in the ventrobasal thalamus of rodents, which do show oscillatory behaviour but are devoid of interneurones [39]. Some findings were also constrained by recordings from slices of the visual thalamus of ferrets, which do have interneurones, but the latter were shown to have little or no participation in oscillatory behaviour [70].

nized, as for the thalamus: each PY cell projected densely to all other PY and IN cells within a local radius of five cells; each IN cell projected to all PY cells within the same local radius (see details in [24]).

2.3. Experimental data

Intracellular recordings and multisite field potential recordings in the thalamus and cerebral cortex of cats in vivo were taken from previous studies, where all experimental details were given (see [14–16, 26]).

3. Results

This study focuses on the cortical control of thalamic circuits, which cellular elements are schematized in *figure 1*. Thalamocortical (TC) relay neurones receive afferent connections from the periphery and project to cortical neurones, mainly in layers I, IV and VI [33]. For the most part, layer VI cortical pyramidal (PY) neurones project back to the same thalamic nucleus from which they receive input, which establishes a topographical arrangement of back-and-forth excitatory connections between thalamus and cortex [39, 63]. Another important element is provided by the thalamic reticular (RE) nucleus, which receives collaterals from the majority of corticothalamic and thalamocortical fibres passing through it (upward and downward arrows in *figure 1*). The RE nucleus in turn projects back to thalamic relay neurones, in a roughly topographical manner, and establishes inhibitory GABAergic terminals but does not project to the cortex [39, 63].

We first examine the effect of cortical synapses on the different cell types in the thalamus, then analyse the impact of corticothalamic inputs at the level of circuits of interconnected thalamic neurones. We next review experimental data showing the decisive effect of corticothalamic feedback on co-ordinating oscillatory behaviour as well as models to explain them.

3.1. Biophysical aspects of corticothalamic feedback

3.1.1. Excitatory synapses on relay cells

We first evaluated the respective impact of cortical and afferent synapses on relay cells. TC cells are characterized by a strong segregation in the distribution of excitatory synapses. Afferent synapses terminate in the proximal region of the dendrites whereas cortical synapses are almost exclusively located in the distal third of the dendritic arbours [44]. We have implemented this segregated distribution by placing afferent and cortical synapses in the proximal and distal thirds of the

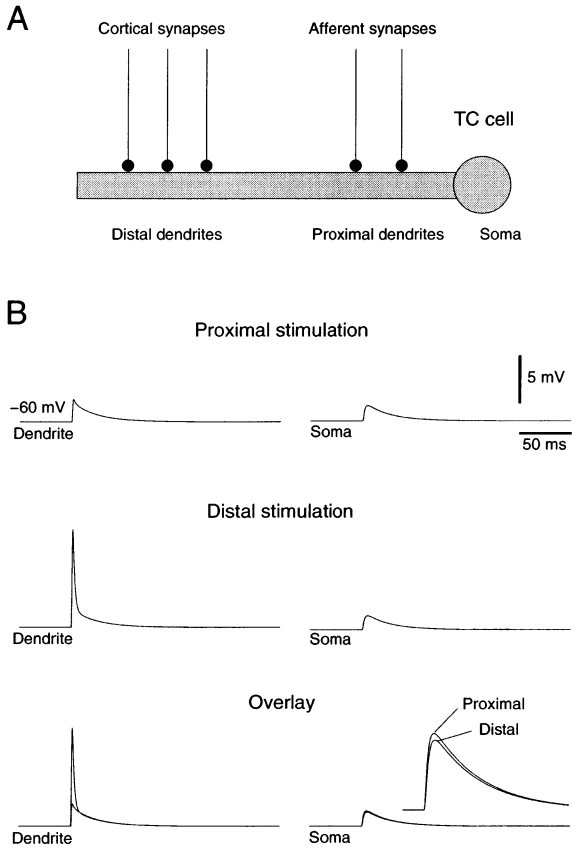

Figure 3. Afferent and cortical EPSPs in a model thalamic relay cell. **A**, Scheme of the excitatory synapse distribution used in the model (same geometry as in *figure 2A*). Cortical synapses were located in the distal third of the dendritic tree, whereas afferent synapses were located in the most proximal third of the dendrites. **B**, EPSP obtained in the soma from activating AMPA/NMDA receptors in an afferent synapse (Proximal stimulation) compared to a cortical synapse (Distal stimulation). The synaptic stimulations produced a higher voltage deflection in the dendrite compared to the soma, resulting in voltage attenuation which was of 48% for the proximal synapse and 600% for the distal stimulation. The superimposition of afferent and cortical EPSPs (Overlay) shows that they had similar amplitude, decay kinetics and time-to-peak at the soma (the total conductance was identical for both EPSPs and was of 5 nS). However, a higher resolution overlay (inset; 200% in time, 500% in amplitude) shows that the amplitude of the proximal EPSP was about 8% larger than the distal EPSP.

dendrites, respectively (schematized in *figure 3A*); all synapses were mediated by AMPA and NMDA receptors (see Methods).

The EPSPs obtained in the soma following activation of AMPA/NMDA receptors in these different dendritic regions are illustrated in *figure 3B*. For afferent synapses, the voltage deflection at the dendritic site was significantly larger than in the soma (*figure 3B*, Proximal stimulation), revealing a voltage attenuation of about 48%. The attenuation was more severe for cortical synapses (*figure 3B*, Distal stimulation), which attained 600% in this case (the attenuation of other distal dendritic sites could be up to 900% in the particular cell geometry shown in *figure 2A*). There is therefore a severe voltage attenuation of synaptic events occurring at distal sites, consistent with previous modelling studies of TC cells [7, 53].

However, despite significant voltage attenuation, the 'current' attenuation was much smaller, as indicated by the similar amplitude of proximal and distal EPSPs in the soma (*figure 3B*, right panels and overlay). Afferent and cortical synapses, activated with the same synaptic conductance (5 nS in this case), led similar amplitude, kinetics and timing of the EPSP at the soma. Their amplitude differed by only 8% in this case (*figure 3B*, inset). We therefore conclude that in relay cells, EPSPs arising from activation of corticothalamic synapses can mimic to some degree the characteristics of the EPSPs from afferent synapses.

A consequence of this property is that the combination of cortical and afferent EPSPs can lead to action potential discharge, with cortical synapses somehow 'complementing' the effect of afferent synapses. This aspect was examined in more detail in *figure 4*. A TC cell was simulated when receiving a sub-threshold afferent EPSP distributed in proximal dendrites. The minimal conductance necessary to complement this initial EPSP to discharge the TC cell was compared for additional excitatory conductances distributed at afferent synapses (Proximal EPSP) or at cortical sites (Distal EPSP). The values obtained were plotted as a function of each other (*figure 4*). For example, with an initial sub-threshold EPSP of 38 nS, this 'complement' conductance was of about 38 nS proximally, whereas if the same initial EPSP was complemented by cortical synapses, the complement conductance had to be of about 35 nS, which defines a point at (38,35) in *figure 4*. This procedure was repeated for initial EPSPs of different conductances. Most points lie along the identity line (*figure 4*, circles), indicating that cortical EPSPs

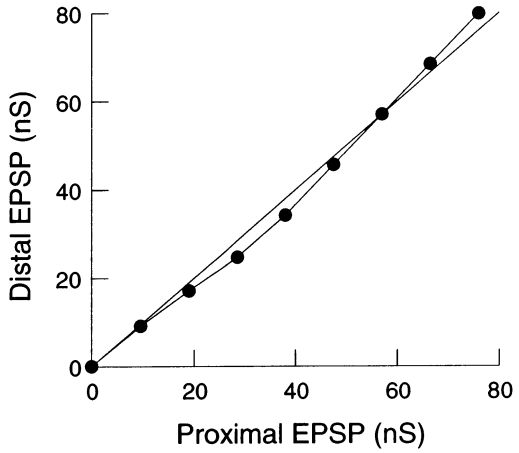

Figure 4. Complementation between afferent and cortical EPSPs in a thalamic relay cell. Simulations similar to *figure 3*, in which two EPSPs were combined to discharge the cell. The 'complement' excitatory conductance needed to discharge the cell was compared for afferent synapses (Proximal EPSP) and cortical synapses (Distal EPSP). These two complement conductances were represented as a function of each other, which defines one point in this graph. The procedure was repeated for EPSPs of different conductances. Most points lie along the identity line, indicating that cortical EPSPs are as efficient as afferent EPSPs to discharge the cell. They can therefore act to complement the afferent information in order to evoke action potential discharge and thereby facilitate the relay to cortex.

are approximately as efficient as afferent EPSPs to complement an afferent excitation. They can therefore act to complement the afferent information in order to evoke action potential discharge and thereby facilitate the relay to cortex.

This protocol was chosen because it reveals another interesting effect: not only afferent and cortical EPSPs seem equally efficient, but close examination of *figure 4* reveals that cortical EPSPs are even more efficient than proximal EPSPs within some range of conductance (between 20 and 50 nS). This facilitatory effect is surprising because isolated cortical EPSPs are more attenuated than afferent EPSPs (see *figure 3*, Overlay) due to their more distal localization[2]. A possible explanation for this facilitatory effect is illustrated in *figure 5*. If only afferent synapses are activated (Proximal only), the current flows towards the soma (rightward arrow) but also through the distal dendrites (leftward arrow). When afferent and cortical

[2] Note that *figure 3* deals with EPSPs at a single dendritic site while *figure 4* describes the effect of a large number of excitatory synapses distributed in the entire dendritic tree.

EPSPs occur together (Proximal + distal), the net current flow is towards the soma, because the entire dendritic tree is depolarized in unison. The cortical synapses therefore augment the efficiency of afferent synapses by optimizing the current flow to the soma.

3.1.2. Inhibitory synapses on TC cells

Thalamic relay cells not only receive excitatory synapses, but are also contacted by inhibitory neurones such as RE cells. The inhibition of TC cells is particularly interesting because these cells contain a low-threshold calcium current (I_T) and can therefore generate burst of action potentials in rebound to IPSPs. There is evidence that I_T is mostly located in dendrites [28, 52, 74, 75], so are inhibitory synapses, which seem to follow a uniform dendritic distribution [41, 44]. To investigate how these dendritic conductances affect rebound burst generation, we have simulated the kinetics and dendritic location of I_T (same model as in [28]) as well as the uniform distribution of $GABA_A$ receptors in the dendrites (see scheme in *figure 6A*). For a given IPSP amplitude, rebound bursting activity was only obtained within a given range of membrane potential (*figure 6B*). This behaviour is expected from the voltage-dependence properties of I_T. The main effect of having IPSPs and I_T located in dendrites is that the threshold IPSP for rebound burst generation was lower, due to the higher local input resistance in dendrites, and therefore the cell was more sensitive to IPSPs (compared to a model with IPSPs and I_T located in the soma; not shown).

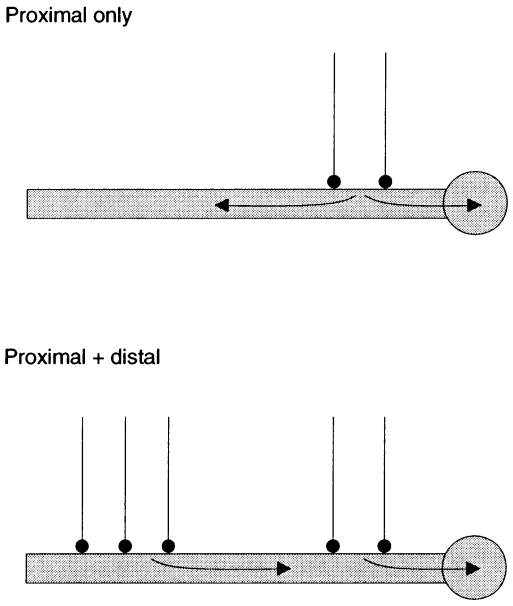

Figure 5. Possible explanation for the facilitatory effect of cortical EPSPs on TC cells. If only afferent synapses are activated (Proximal only), the current flows towards the soma (rightward arrow) but also through the distal dendrites (leftward arrow). When afferent and cortical EPSPs occur together (Proximal + distal), the net current flow is towards the soma, because the entire dendritic tree is depolarized in unison. The cortical synapses therefore augment the efficiency of afferent synapses by optimizing its current flow to the soma.

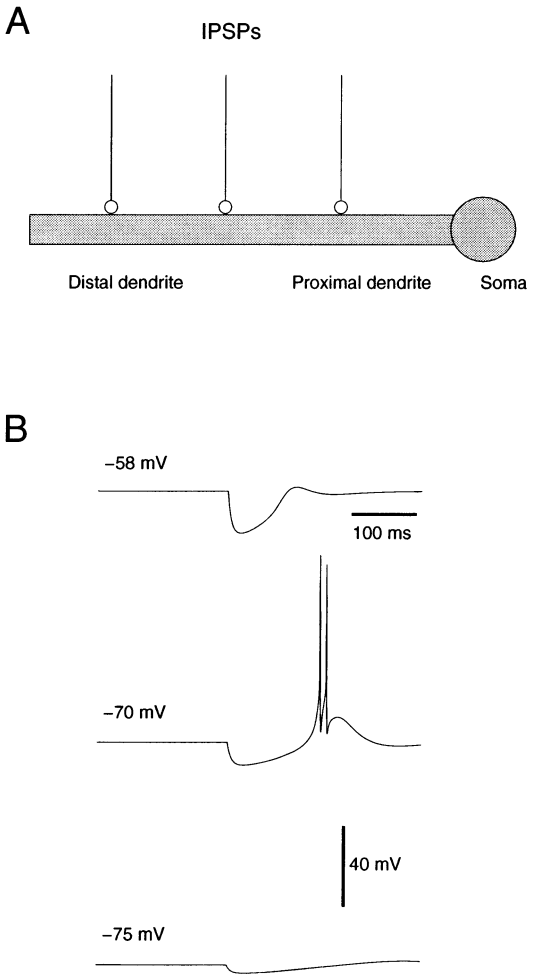

Figure 6. Voltage-dependence of IPSP-rebound sequences in a model thalamic relay cell. **A**, Scheme indicating that IPSPs were distributed uniformly in the dendrites of the modelled TC cell (same geometry as in *figure 2A*). **B**, IPSP obtained in the soma from activating dendritic $GABA_A$ receptors (total conductance of 10 nS). The tree traces show the effect of the same GABAergic conductance at three different resting membrane potentials. For a fixed IPSP amplitude, rebound bursting activity was only obtained within a definite range of membrane potential, because of the activation kinetics of the low-threshold calcium current I_T. The kinetics and dendritic location of I_T were modelled as in [28].

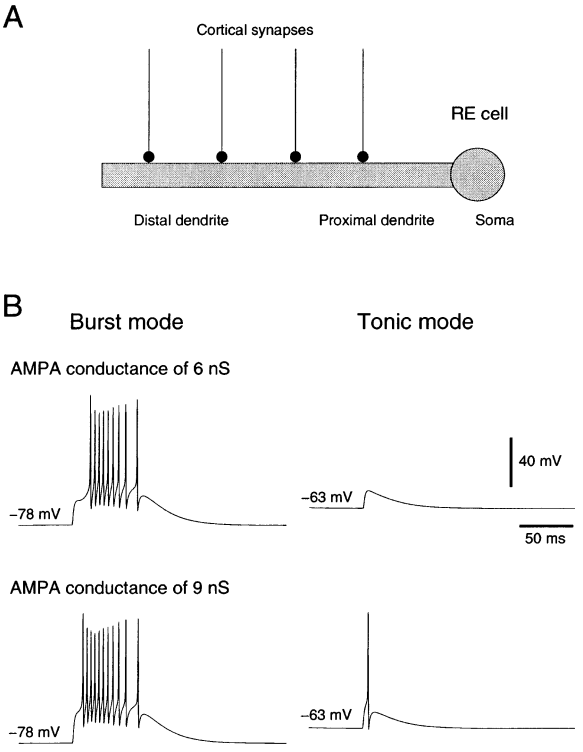

Figure 7. Voltage-dependence and sensitivity of bursting activity in a model thalamic reticular cell. **A**, Scheme indicating that EPSPs were distributed uniformly in the dendrites of the modelled RE cell (same geometry as in *figure 2B*). **B**, Simulations obtained at two different resting membrane potentials (-63 and -78 mV, obtained by manipulating K^+ leak conductances) and two different total EPSP conductance (6 nS, upper traces; 9 nS, lower traces). Both EPSPs led to a burst discharge at -78 mV, but only the 9 nS-EPSP generated an action potential at -63 mV, indicating a higher excitability when the dendrites are hyperpolarized. Model identical to that described in [23].

3.1.3. Excitatory synapses on RE cells

Another main class of thalamic cell, RE neurones, may also have high densities of T-current in their dendrites [23]. However, contrary to TC cells, RE cells generate bursts following EPSPs [4, 5]. Because it has been discovered that RE cell dendrites have a particularly high density of excitatory synapses of cortical origin [45], it may be that EPSPs interact locally with I_T in dendrites. To investigate this type of interaction, we have simulated a model of thalamic RE cell with dendritic I_T obtained previously [23]. Excitatory synapses (AMPA/NMDA) were distributed uniformly in dendrites (see scheme in *figure 7A*). Like TC cells, the genesis of bursts was voltage-dependent. Simulated EPSPs successfully generated bursts if the dendrites were sufficiently hyperpolarized (*figure 7B*). The exact voltage range at which bursts occurred depended on the strength of the EPSP, as expected from the voltage-dependent kinetics of I_T.

Perhaps the most interesting feature of the dendritic interactions underlying RE bursts is that the presence of T-current in the dendrites gives to the RE cell an exquisite sensitivity to cortical EPSPs. This is shown in *figure 7B*, in which the left and right panels compare the effect of the same EPSP at two different membrane potentials. If the dendrites of the RE neurone were depolarized by blocking leak K^+ conductances, mimicking the action of some neuromodulators on these cells [47], these EPSPs were sub-threshold or evoked single spikes. On the other hand, when the membrane potential was more hyperpolarized (-78 mV in *figure 7B*), the same EPSPs generated a full-blown burst of action potentials, although the input resistance of the cell was smaller. The same corticothalamic excitation therefore evokes a radically different output of the RE nucleus according to the state of its dendrites.

Here again, this effect is caused by local dendritic interactions. Because of the high local input resistance in dendrites, EPSPs of relatively small conductance are capable of activating I_T and initiating a regenerative process that invades the entire dendritic tree and generates a burst of action potentials. This process however only takes place when the membrane is sufficiently hyperpolarized. At depolarized membrane potentials, I_T is inactivated, and the dendrites behave as if they were passive. In this case, regenerative burst activity do not occur and the cell responds to EPSPs by producing single spikes, as shown in *figure 7*.

3.1.4. Corticothalamic influence on thalamic circuits

The above simulations show that the presence of T-current in the dendrites of thalamic neurones, and the location of synapses in different regions of these dendrites can give rise to a complex range of interactions. We attempt to integrate these interactions into circuits of interconnected thalamic neurones subjected to corticothalamic feedback. The circuit involving interconnected TC and RE cells using the dendritic distribution of synapses investigated above is shown in *figure 8A*. Corticothalamic EPSPs were AMPA/NMDA-mediated and were distributed uniformly in RE cells but only in the distal dendrites of TC cells. Excitatory (AMPA-mediated) synapses from TC to RE were uniformly distributed, as were the inhibitory synapses

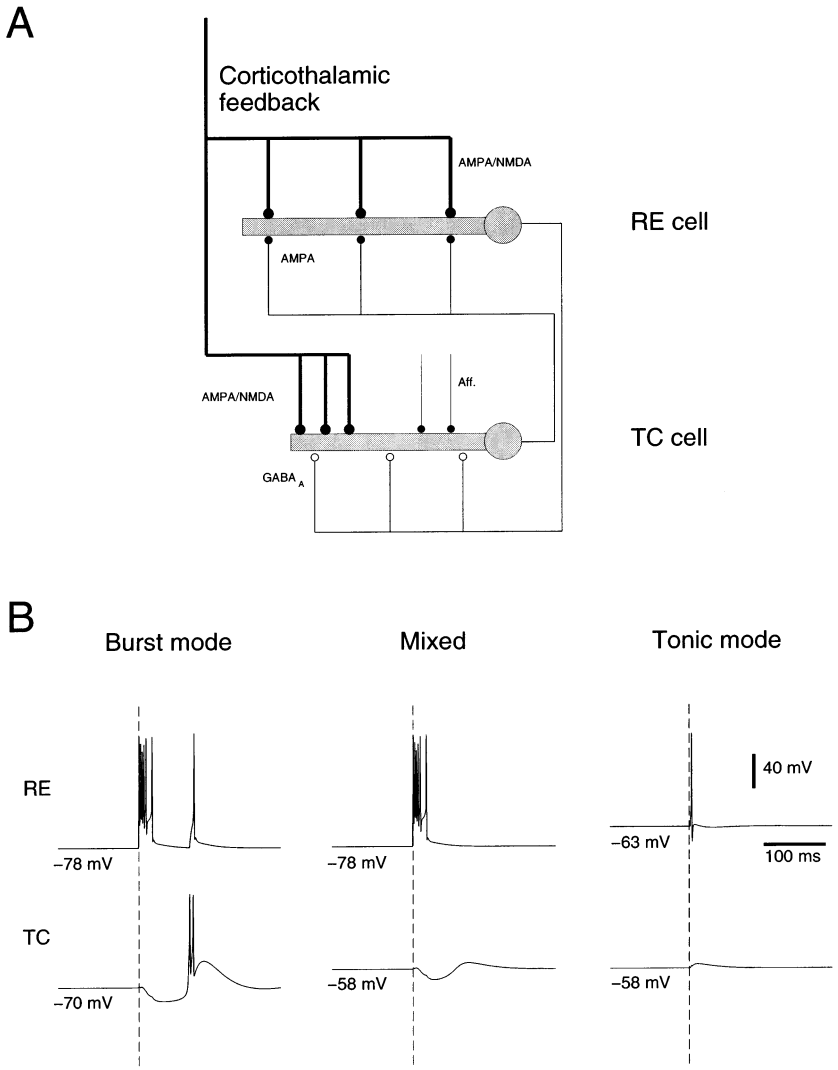

Figure 8. The effect of corticothalamic feedback depends on the state of thalamic neurones. **A**, Scheme of the circuit involving interconnected TC and RE cells using the dendritic distribution of synapses investigated here: cortical EPSPs were AMPA/NMDA-mediated and were distributed uniformly in RE cells but only in the distal dendrites of TC cells. Excitatory (AMPA-mediated) synapses from TC to RE were uniformly distributed, as were the inhibitory synapses ($GABA_A$-mediated) from RE to TC. RE cells also inhibited each-other via $GABA_A$ synapses (not shown). **B**, Response of this circuit to the activation of corticothalamic synapses. When both TC and RE cells were hyperpolarized (Burst mode), cortical EPSPs triggered bursts in RE cells which evoked strong IPSPs in TC cells, followed by rebound. If TC cells were depolarized (Mixed), the IPSP evoked by RE bursting did not lead to rebound bursts. When both cell types were depolarized (Tonic mode), cortical EPSPs evoked single-spike activity in RE cells. In this case only, the direct excitation of corticothalamic EPSPs on TC cells was visible.

($GABA_A$-mediated) from RE to TC. The afferent synapses (Aff.) were located only in proximal dendrites of TC cells.

The response of this circuit to the activation of corticothalamic synapses was highly dependent on the state of thalamic neurones. When both TC and RE cells were hyperpolarized (*figure 8B*, Burst mode), cortical EPSPs triggered bursts in RE cells which evoked strong IPSPs in TC cells, followed by rebound. If TC cells were depolarized (*figure 8B*, Mixed), the IPSP evoked by RE bursting did not lead to rebound bursts. When both cell types were depolarized (*figure 8B*, Tonic mode), cortical EPSPs evoked single-spike activity in RE cells. In this case only, the direct excitation of corticothalamic EPSPs on TC cells was visible.

These simulations therefore show that the net effect of corticothalamic feedback on relay cells is not necessarily facilitatory, as usually assumed, but can be largely inhibitory depending on the state of thalamic reticular neurones. We explore below possible consequences of these interactions at the network level.

3.2. Impact of corticothalamic interactions at the network level

We begin by showing experimental data demonstrating that one of the effects of corticothalamic feedback is to organize large-scale coherent oscillations. We then show how these results can be accounted for in relation to the different interactions described above.

3.2.1. The large-scale coherence of thalamic oscillations depends on corticothalamic feedback

We investigated the influence of the massive corticothalamic projection on the spatiotemporal coherence of spontaneous and global oscillations generated in the cat thalamus under barbiturate anesthesia [14, 16]. Multisite local field potential recordings from the thalamus, using eight equidistant tungsten electrodes, revealed that spindle oscillations were characterized by a remarkable large-scale coherence across 7 mm distance[3] (*figure 9A*). The cortex was then removed by suction ($n = 8$) and the electrodes returned to approximately the same positions. In the decorticated animal, the thalamus still generated spindles, but their occurrence was largely not coincident in time among the different electrodes (*figure 9B*). The evaluation of the decay of intersite correlation as a function of distance (*figure 9C*) shows that removal of the cortex dramatically reduces large distance correlations.

Dual intracellular recordings of thalamic relay cells were also performed in the decorticated thalamus [14] and revealed that within closely located sites (< 1 mm), two TC cells were perfectly synchronized showing that local synchrony was still present in restricted thalamic areas. For larger distances, the two TC cells presented the typical intracellular features of spindle oscillations, but were totally dissociated from each-other [14]. The presence of the cortex is therefore necessary to maintain the coherence over large distances in the thalamus.

A possible explanation for this synchronizing role of the cortex would be that synchrony is attained within cortical circuits due to the abundant horizontal corticocortical projections in areas 5–7 [3] and thereafter imposed on the thalamus. This possibility is however very unlikely because disruption of intracortical connectivity by physically cutting intracortical connections did not disrupt the large-scale coherence of these oscillations [14, 16], while the coherence was markedly decreased following chemically-induced cortical depression [15, 25].

Thus these results indicate that the large-scale coherence does not depend on intrathalamic mechanisms, as proposed by Andersen and Andersson [2], nor on intracortical mechanisms. In the following, we investigate possible mechanisms to account for these observations using computational models.

3.2.2. The role of inhibition in large-scale coherent oscillations

A computational model was introduced to account for the above results based on networks of interconnected thalamic and cortical neurones [24, 25]. This model investigated a mechanism in which the large-scale coherence of oscillations depends on mutual interactions between thalamus and cortex. The main hypothesis of this model was that the net effect of the corticothalamic feedback on thalamic relay cells must be inhibitory. We start by illustrating experimental evidence to support this hypothesis and show how it may account for the experimental results.

We hypothesized that corticothalamic feedback operates on the thalamus mainly by evoking bursts in RE cells, thereby recruiting TC cells through IPSPs that dominate over direct cortical EPSPs (see *figure 8B*, Burst mode). Although there are no quantitative data for the strength of cortical EPSPs on TC and RE cells, intracellular recordings of RE cells consistently show strong EPSPs of cortical origin that produce bursts of action potentials in response to electrical stimulation of appropriate cortical area, even with low stimulus intensities [13, 51]. Stimulation of the internal capsule has similar effects on RE cells in thalamic slices [67]. In contrast, intracellular recordings of TC cells in response to stimulating the anatomically-related cortical area show an EPSP-IPSP sequence dominated by the IPSP component (*figure 10A*). The majority of TC cells recorded in the lateral posterior nucleus (24 out of 26) had IPSP

[3] This distance covers most of the anterior-posterior extent of the cat thalamus and the recordings correspond to different thalamic nuclei.

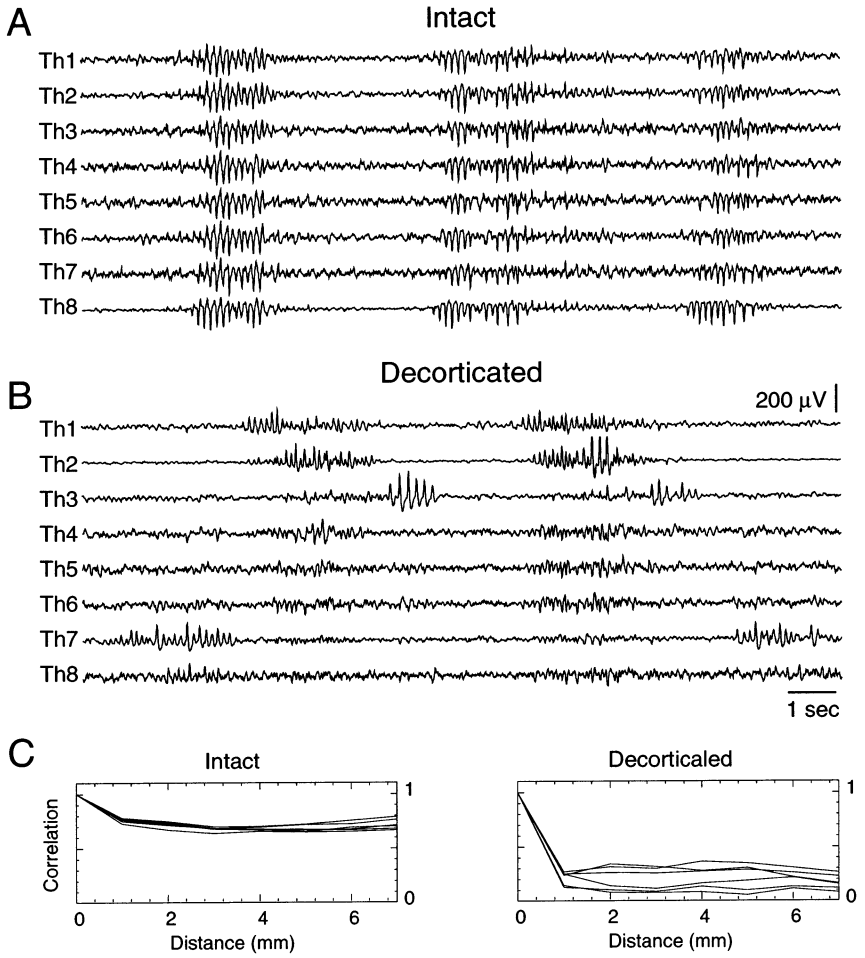

Figure 9. Corticothalamic feedback participates in the genesis of large-scale coherent oscillations. Multiple extracellular recordings were performed in cat thalamus in vivo under barbiturate anesthesia. Eight tungsten electrodes (Th1-Th8) were placed in the anterior-posterior axis of the thalamus over a distance of 7 mm (inter-electrode distance of 1 mm). In control conditions (Intact), the recorded thalamic area produced synchronous spindle oscillations. After removal of the cortex (Decorticated), each location continued to generate spindle oscillations, but the large-scale coherence was lost. The lower panels show the decay of intersite correlation with distance for six different consecutive epochs of 20 s, demonstrating that removal of the cortex dramatically reduces correlations over large distances. Modified from [14].

amplitudes of 11.1 ± 1.2 mV (mean $\pm$ SE) at -60 mV ($n = 26$). An EPSP was not apparent in a few cells ($n = 5$), but IPSPs always occurred. Cortical stimulation was able to fire the TC cell through EPSPs at the resting membrane potential (-62.3 ± 1.5 mV) only occasionally ($n = 2$).

Possible mechanisms for such inhibitory dominance in TC cells were investigated above based on models incorporating the dendritic location of synapses (*figure 8B*). In simpler circuits consisting of single-compartment thalamic neurones (see details in [24]), with two TC cells interconnected with two RE cells (see scheme in *figure 10B*), the EPSP/IPSP sequence observed experimentally could be reproduced provided that the cortical EPSPs on RE cells were stronger than the EPSPs on TC cells. In *figure 10B*, the conductance of AMPA-mediated cortical drive on TC and RE cells, as well as the $GABA_A$-mediated IPSP from RE cells were of the same order of magnitude. In this case, cortical EPSPs were shunted by reticular IPSPs and cortical stimulation did not evoke oscillations in the thalamic circuit. In contrast, when the EPSPs on TC cells had smaller conductances (from 5–20 times) the EPSP-IPSP sequence was similar to intracellular recordings and cortical stimulation was effective in evoking oscillations (*figure 10C*). The exquisite sensitivity of RE neurones to cortical

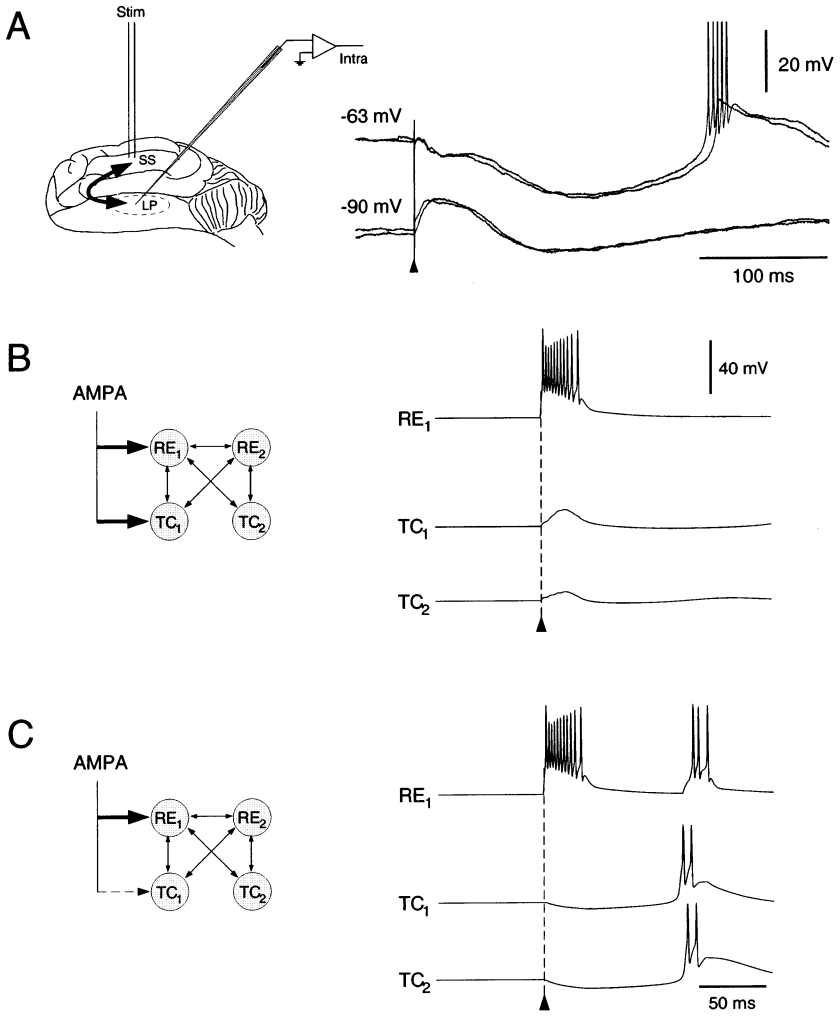

Figure 10. Inhibitory dominance of corticothalamic feedback during barbiturate anesthesia. **A**, Intracellular recording of a thalamic relay cell in the lateral posterior (LP) thalamic nucleus while stimulating the anatomically-related part of the suprasylvian (SS) cortex in cats during barbiturate anesthesia. Cortical stimulation (arrow) evoked a small EPSP followed by a powerful biphasic IPSP. The IPSP gave rise to rebound bursts in that cell. This case was representative of the majority of recorded TC cells. **B**, Simulation of corticothalamic feedback EPSPs in a circuit of four interconnected thalamic cells. Cortical (AMPA-mediated) EPSPs were stimulated by delivering a presynaptic burst of four spikes at 200 Hz to AMPA receptors. The maximal conductance was similar in TC and RE cells (100 nS in this case) and no rebound occurred following the stimulation (arrow). **C**, Same simulation with dominant IPSP in TC cell. In this case, the AMPA conductance of stimulated EPSPs in the TC cell was dropped down to 5 nS. The stimulation of AMPA receptors evoked a small EPSP followed by strong IPSP, then by a rebound burst in the TC cells, as observed experimentally. Modified from [24].

EPSPs (see *figure 7*) could therefore be simulated in single-compartment models by using stronger excitatory conductances in RE cells[4].

Inhibitory dominance is compatible with previous intracellular recordings in vivo. First, the dominance of inhibition has been previously observed in various thalamic relay neurones following stimulation of related cortical area [1, 10, 12, 18, 43, 55, 73]. Second, this EPSP-IPSP sequence is transformed into a more powerful EPSP after lesioning the RE nucleus [18]. Third, spindle oscillations can be robustly evoked by stimulating the cortex (even

[4] For weak EPSP conductances in RE cells, the cortical feedback evoked no burst activity, whereas larger cortical EPSPs evoked bursts in RE cells consistent with the picture shown in *figure 7*.

contralaterally to avoid backfiring of TC axons and collateral activation of RE cells; see [12, 55, 65]). Fourth, during spontaneous oscillations, TC cells are entrained into the oscillation by an initial IPSP but rarely by initial EPSPs [60]. Fifth, dominant IPSPs were also observed with other anesthetics, such as ketamine-xylazine [68].

Thalamocortical network models were investigated to determine how cortical feedback could organize the coherence of thalamic oscillations that were observed experimentally. The most striking feature was that the activity in individual thalamic cells as well as local average potentials were considerably more coherent in the presence of cortical feedback (*figure 11*): The left panel shows several spindle sequences in the thalamocortical network (see details in [24]). The right panel shows the same simulation with cortical cells removed. Without cortical feedback, different initiation sites for spindles were not co-ordinated. Some of them remained local, others gave rise to systematic propagation of oscillations from one side of the network to the other (*figure 11B*, bottom right panel).

It was critical that cortical feedback recruited TC cells through dominant inhibition to produce this effect. The presumed mechanism is a 'reset' of the modulation mechanisms intrinsic to TC cells (upregulation of I_h current) that are responsible for the waxing and waning patterns. The IPSP-dominated synaptic feedback is an ideal mechanism to recruit I_h in TC cells. During spindle oscillations starting with such synchronized cortical feedback, the individual upregulation mechanisms of I_h in TC cells tend to synchronize such that several TC cells restart oscillating at roughly the same time, leading to several near-simultaneous initiation sites for spindles (see details in [24]).

The difference in spatiotemporal coherence was also apparent from spatial correlations. Similar to experiments, spatial correlations from thalamic cells showed a more pronounced decay with distance when cortical feedback was removed compared to the intact thalamocortical network (*figure 11C*).

3.2.3. The large-scale coherence of other oscillation types

The large-scale coherence of spindle oscillations (*figure 9A*) is not necessarily representative of all oscillation types in the thalamocortical system. We show here that in unanesthetized animals, several oscillation types display different properties of large-scale coherence and suggest how the above considerations on corticothalamic interactions may help to explain these observations.

Multisite local field potentials (LFPs) were recorded using a set of eight equidistant bipolar electrodes in the cerebral cortex (suprasylvian gyrus) of unanesthetized cats. Wake/sleep states were identified using the following criteria: Wake: low-amplitude fast activity in LFPs, high electrooculogram (EOG) and high electromyogram (EMG) activity; Slow-wave sleep: LFPs dominated by high-amplitude slow-waves, low EOG activity and EMG activity present; REM sleep: low-amplitude fast LFP activity, high EOG activity and abolition of EMG activity. During waking and attentive behaviour, LFPs were characterized by low-amplitude fast (15–75 Hz) activity (*figure 12A*, Awake). During slow-wave sleep, LFPs were dominated by high-amplitude slow-wave complexes occurring at a frequency of <1 Hz (*figure 12B*, Slow-wave sleep). Slow-wave complexes of higher frequency (1–4 Hz) and spindle waves (7–14 Hz) were also present in slow-wave sleep. During periods of REM sleep, the activity was similar to waking periods (*figure 12C*, REM sleep).

Correlations represented as a function of distance revealed marked differences of large-scale coherence between awake/REM and slow-wave sleep (*figure 12*, right panels). Slow-wave sleep episodes display slow-wave complexes of a remarkable spatiotemporal coherence, as indicated by the high values of spatial correlations for large distances, in contrast with the steeper decline of spatial correlations with distance during wakefulness and REM sleep. Spatial correlations were evaluated in different animals and during different wake/sleep episodes in the same animals and showed consistent behaviour similar to *figure 12* (see details in [26]).

This analysis shows that slow-wave sleep and awake/REM states are distinguished by the behaviour of correlations with distance. Slow-wave sleep is spatially coherent and is characterized by high values of correlations across cortical distances of several millimetres. Wake and REM sleep show less spatial coherence, with correlations decaying steeply with distance.

3.2.4. Hypothetical mechanism to explain local coherence

As shown above, it is possible to account for the large-scale coherence of slow oscillations based on reciprocal corticothalamic interactions. Similarly, if fast oscillations in cerebral cortex are generated

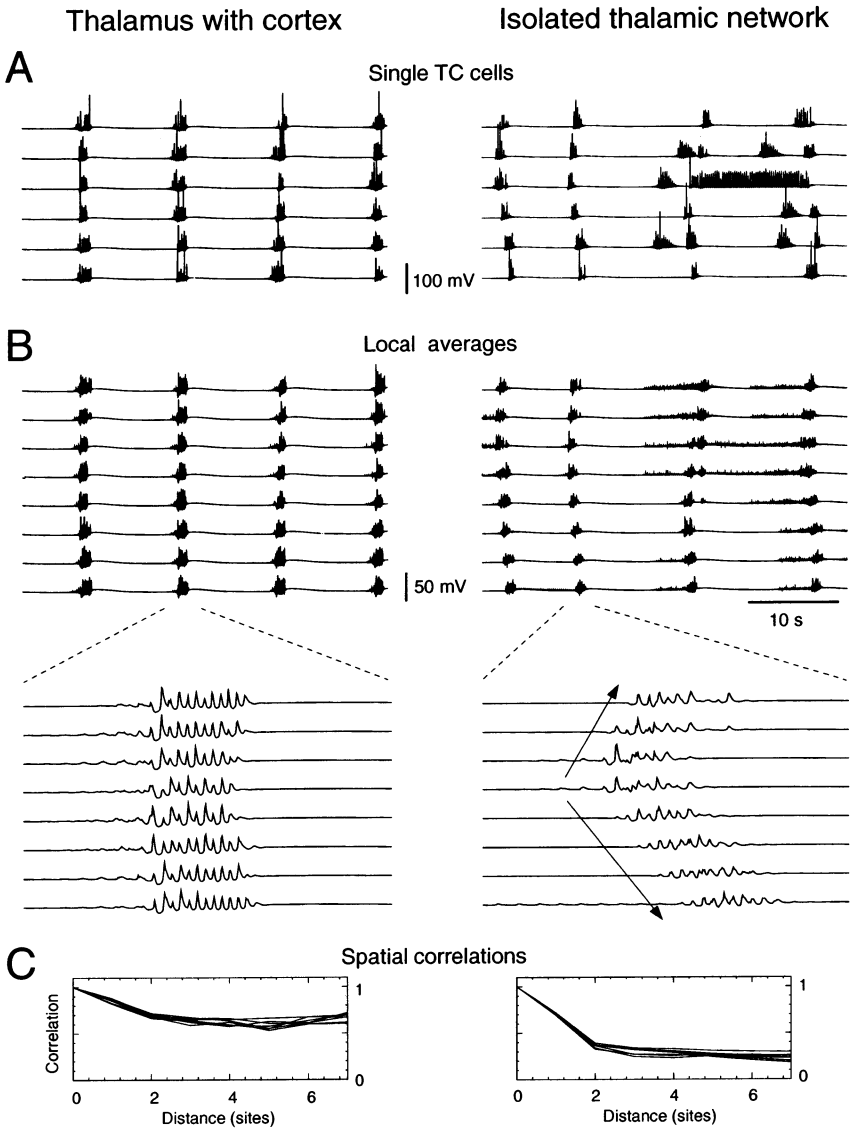

Figure 11. The large-scale coherence of spindle oscillations in model thalamic networks is critically dependent on corticothalamic feedback. Spontaneous spindles are shown in the presence of the cortex (left panels) and in an isolated thalamic network (right panels) taken in the same conditions. **A**, The same six equally spaced TC cells are shown during spindle oscillations in both networks. **B**, Local averages calculated from twenty-one adjacent TC cells, taken at eight equally spaced sites on the network. The bottom graphs represent a representative spindle at 10 times higher temporal resolution. The near-simultaneity of oscillations in the presence of the cortex is contrasting with patterns of systematic propagation in the isolated thalamic network (arrows). **C**, Spatial decay of intersite correlations calculated from local averages. The presence of corticothalamic feedback was necessary to maintain high correlations across large distances. Modified from [24].

by networks of local inhibitory interneurones [11, 69], and because inhibitory neurones only establish short-range connections [66], it is conceivable that the coherence of these oscillations would extend over short cortical distances, as observed in vivo (see *figure 12*; see also [9, 62]).

However, although mechanisms could be conceived to explain the coherence of different oscillation types, a fundamental question still remains unanswered: how can these different types of coherence coexist in the same network? A model was proposed to explain these variations of coherence

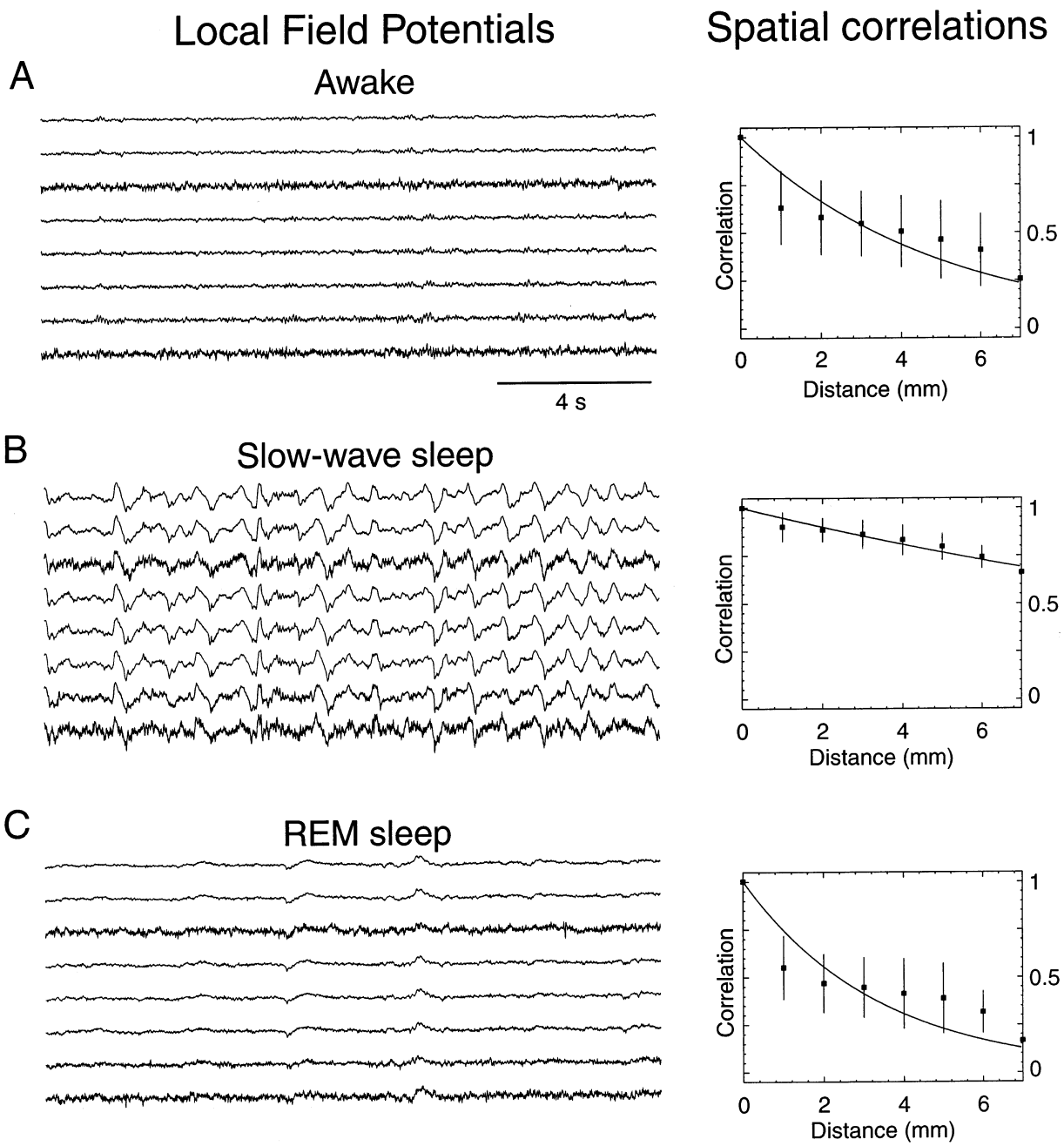

Figure 12. Multisite local field potentials in cat cerebral cortex during natural wake and sleep states. Eight bipolar electrodes (interelectrode distance of 1 mm) were inserted into the depth (1 mm) of areas 5-7 of cat neocortex (suprasylvian gyrus, area 5-7). Local field potentials (LFPs) are shown (left panels) together with a representation of the correlations as a function of distance (Spatial correlations; right panels). **A**, When the animal was awake, LFPs were characterized by low-amplitude fast activities in the beta/gamma frequency range (15–75 Hz). Correlations decayed steeply with distance. **B**, During slow-wave sleep, the LFPs were dominated by large-amplitude slow-wave complexes recurring at a slow frequency (< 1 Hz; up to 4 Hz). Correlations stayed high for large distances. **C**, During episodes of REM sleep, LFPs and correlations had similar characteristics as during wake periods. Modified from [26].

based on two-dimensional networks of excitatory and inhibitory neurones subject to pacemaker inputs of various frequencies [20]. Although this model displayed low-frequency oscillations with large coherence and fast oscillations with low coherence, it did not include the important role of corticothalamic feedback. We would like to propose here a more plausible hypothesis, based on reciprocal corticothalamic interactions (*figure 13*). When thalamic neurones are hyperpolarized (Burst mode), a localized cortical discharge evokes bursts in a large area of the thalamus, which in turn recruits a still-larger area of TC cells through IPSPs (*figure 13*, light gray in Burst Mode). In this case, as shown above, the burst discharge of RE cells evokes strong IPSPs in TC cells, which overwhelm the direct cortical EPSPs. This property of 'inhibitory dominance' can explain the genesis of large-scale coherent slow oscillations, such as sleep spindles [24].

We hypothesize that this type of corticothalamic interaction may be reversed when thalamic neurones are depolarized, as indicated above (see *figure 8*). In this case, the same cortical discharge does not evoke bursts in RE cells, therefore the direct cortical EPSPs now compete with a much smaller IPSP component such that the EPSP may dominate. The consequence is that the cortex recruits directly TC cells with excitation (*figure 13*, dark gray in Tonic Mode). This 'excitatory dominance' results in a much more focused corticothalamic feedback and finer topographic interactions between thalamus and cortex, which could promote local synchrony in the network. By changing the resting level of thalamic neurones, the same thalamocortical circuits would be capable of generating low-frequency oscillations with large-scale coherence, as well as fast oscillations with local coherence. Computational models are presently under investigation to test this hypothesis.

4. Discussion and conclusion

In this paper, we have investigated the effect of cortical synapses on thalamic cells and circuits, as well as the role of corticothalamic feedback in co-ordinating oscillatory activity in the thalamocortical system. We discuss here possible implications and predictions of these models and possible ways to test them experimentally.

4.1. The impact of corticothalamic feedback on relay neurones

One of the main prediction of the model is that afferent and cortical synapses evoke excitatory synaptic potentials of similar amplitude, kinetics and timing at the soma of relay cells (*figure 3*). Previous studies have shown that synaptic potentials in TC cells display a significant voltage attenuation [7, 53]. The voltage attenuation was present in this model, but it was mainly due to the high local input resistance in dendrites, causing high local voltage deflections (see dendritic sites in *figure 3*), but the EPSP seen at the soma showed little variations with the position of the synapse in the dendritic tree.

Several factors could affect this conclusion. First, the glomerular structure of afferent synapses in relay cells (see [39]) was not taken into account here. However, these glomeruli are only present in thalamic nuclei containing interneurones, which was not the case for the ventrobasal nucleus of the rat, in which the cell studied here was obtained [38]. Second, metabotropic receptors have been described in LGN and reticularis neurones [17, 71], but were not incorporated here. These receptors however require prolonged or repetitive stimulation to be activated [71], which should not affect the present conclusions based on isolated stimuli.

The consequence of the similarity between cortical and afferent EPSPs is that corticothalamic inputs seem capable of complementing the sensory information at the level of relay cells. The descending corticothalamic information could therefore be a 'prediction' of the sensory input. This is consistent with the previously proposed idea that a very significant part of thalamocortical processing occurs within corticothalamic loops, while sensory information provides a modulation of this intrinsic activity [46]. The similarity between cortical and afferent EPSPs in model TC cells, together with the fact that corticothalamic synapses largely outnumber sensory synapses [29, 30, 44, 45], seem compatible with this view.

4.2. The different types of corticothalamic feedback

At the level of thalamic circuits, the investigation of the effect of cortical EPSPs revealed several types of corticothalamic interactions based on the state of thalamic neurones. When both TC and RE cells are in the bursting mode, the bursts of action potentials of RE cells evoke powerful IPSPs which

overwhelm the direct cortical EPSPs in TC cells, resulting in a dominant inhibitory effect of corticothalamic feedback on relay cells (*figure 8B*, Burst mode). This 'inhibitory dominance' is a characteristics which has been consistently observed experimentally [1, 10, 12, 18, 43, 55, 73].

The corticothalamic influence may be radically different if both thalamic cell types are in tonic firing mode. In this case, cortical EPSPs evoke single-spike activity in RE cells, which evoke small feedforward IPSPs in TC cells. Cortical EPSPs now compete with a much smaller IPSP component and the net influence of the cortex may therefore be excitatory on relay cells (*figure 8B*, Tonic mode). This is consistent with experimental observations that the effect of corticothalamic feedback on relay cells can be excitatory [1, 57, 59, 71, 73].

The model further indicates that the state of RE cell dendrites is the main factor determining the excitatory vs. inhibitory nature of the cortical influence on relay cells, and therefore the gating of information to the cerebral cortex. At the level of single RE cells, the model has shown that the presence of high densities of T-current in dendrites is responsible for an exquisite sensitivity to cortical EPSPs if these dendrites are hyperpolarized (*figure 7*). In this case, RE cells generate bursts that evoke a powerful inhibition in relay cells, which antagonizes the relay of information. On the other hand, with depolarized dendrites, RE cells generate single spikes and the direct cortical EPSPs now dominate in relay cells, which would favour the relay of information. The picture that emerges is that, according to the state of RE cells' dendrites, the corticothalamic feedback can act in favour or against the relay of information.

Is it possible that controlling the burst mode of RE cells is an important factor in attentional mechanisms? The state of RE cells has been shown to be controlled by various neuromodulators, some of which lead to depolarization while others hyperpolarize RE cells [47]. In particular, acetylcholine, which is implicated in the ascending control of arousal, hyperpolarizes RE cells by

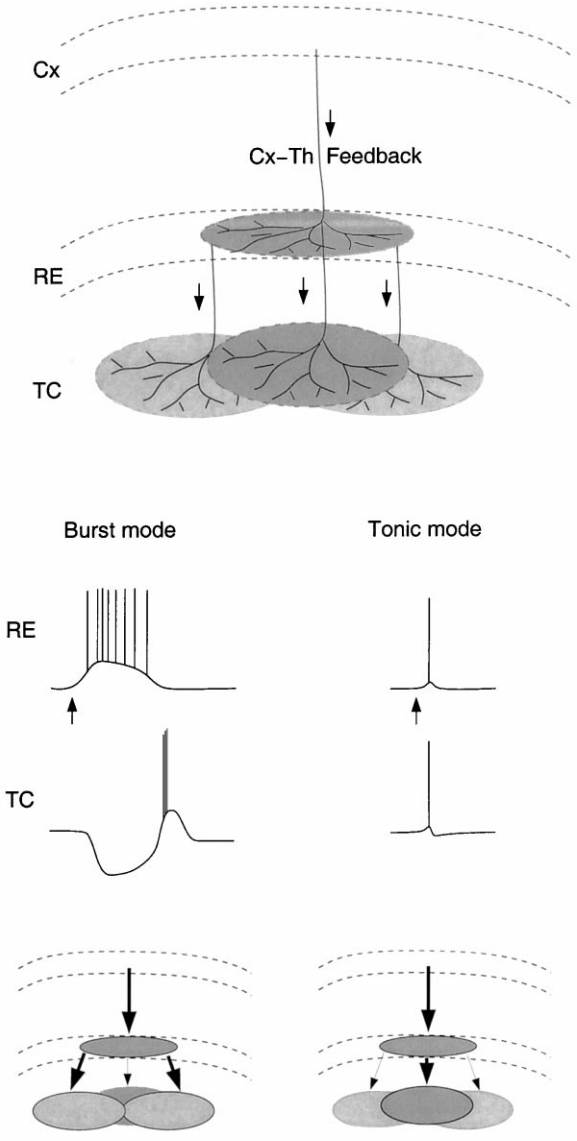

Figure 13. Illustration of the hypothesis that corticothalamic feedback controls thalamic relay cells in a state-dependent fashion. Top, Scheme of the extent of axonal collaterals of corticothalamic fibres (dark grey) which arborize both in the thalamic reticular (RE) nucleus and in thalamic relay nuclei (TC). The axon arborization of two RE cells projecting to the same relay nucleus are indicated in light grey. Bottom, Illustration of how corticothalamic interactions may critically depend on the state of thalamic neurones. Left panels, During slow-wave sleep or barbiturate anesthesia, thalamic cells are in burst mode and cortical volleys recruit large burst discharges in RE cells, which mediate powerful IPSPs in TC cells. The net effect of corticothalamic feedback on relay cells is therefore a dominant inhibition, which is widespread in the thalamus (bottom scheme). Models have shown that this widespread dominant inhibition may explain the large-scale coherence of oscillations during barbiturate anesthesia and slow-wave sleep [24, 25]. Right panels, During activated states (wakefulness or REM sleep), thalamic neurones are in tonic firing mode. In this case, cortical volleys evoke single-spike activity in RE cells and a dominant excitatory effect on relay cells. This 'excitatory dominance' is also relatively focused (bottom scheme), which may explain why fast oscillations are coherent only within narrow cortical and thalamic sites, although generated by the same network.

activating leak K^+ conductances and promotes burst firing [48]. On the other hand, noradrenaline, another neuromodulator implicated in arousal, has opposite effects on RE cells [49]. The burst mode of RE cells therefore seems to be modulated differentially by various neurotransmitters and may have a particular significance during aroused states. The model has shown that when RE cells are in the burst mode while TC cells are in the tonic mode, the corticothalamic feedback evokes IPSPs with no rebound (*figure 8B*, Mixed). The action of acetylcholine on thalamic circuits would favour this latter type of interaction, therefore acting against the relay of information.

The significance of such interactions should be investigated by future experiments and models. For example, it should be possible to investigate the effect of stimulating corticothalamic fibres in thalamic slices, in parallel with the application of neuromodulators such as acetylcholine and noradrenaline. In vivo experiments should investigate corticothalamic interactions while clearly identifying the state (bursting vs. tonic) of the different thalamic cell classes[5]. It is certain that understanding the multiple facets of corticothalamic interactions will require a combination of experimental approaches and computational models that integrate the various receptor types present in these circuits.

4.3. Consequences at the network level

We have also shown that the effect of corticothalamic feedback is to co-ordinate the genesis of widespread, coherent oscillations across different thalamic and cortical areas [14, 16] (see *figure 9*). Computational models have shown that the inhibitory dominance of corticothalamic interactions is the most determinant factor to explain these observations [24]. The mechanism for the genesis of large-scale coherence involves corticothalamic loops which recruit large thalamic areas through the RE nucleus and synchronizes the entire thalamocortical network in a few oscillation cycles [24]. The apparently contrasting experimental observations that spindle oscillations propagate in slices [40] while they are coherent across large distances in vivo [2, 14, 16] can be explained by this mechanism. The state of thalamic cells, which are in bursting mode during these oscillations, is also consistent with the above considerations on inhibitory dominance.

The thalamocortical system is however capable of generating other oscillation types which display different levels of spatiotemporal coherence (*figure 12*). In particular, fast oscillations during wakefulness or REM sleep are considerably less coherent than the slow oscillation types. Because these fast oscillations may be generated by local circuits of interneurones [11, 69], it is possible to explain their low coherence based on intracortical interactions. However, when taking into account corticothalamic loops, the existence of locally coherent oscillatory states implies that interactions between cortex and thalamus must follow a topographic focused scheme. We have proposed here how modulating the state of thalamic neurones can provide two fundamentally different modes of corticothalamic interactions (*figure 13*). The burst mode is ideal for generating large-scale coherent oscillations, while the tonic mode favours local and focused bidirectional interactions between thalamus and cortex.

[5] Intracellular measurements of the effect of cortical feedback on relay cells are usually obtained under anaesthesia, in which case thalamic neurones are in the bursting mode. Future experiments should investigate the effect of cortical feedback in brain-activated states, such as during wakefulness or following stimulation of the brain stem in anaesthetized animals.

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